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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/681,418 | 10/07/2003 | H. Michael Shepard | NB 2008.01 | 7416 |

23639 7590 03/15/2004

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| EXAMINER | |
|---|---|
| CRANE, LAWRENCE E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1623 | |

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/681,418 | SHEPARD ET AL. | |
| | Examiner | Art Unit | |
| | L. E. Crane | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10/07/03(amdts A & B)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *53-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq. ID Req.*.

The Abstract of the Disclosure is objected to because the abstract is not in standard USPTO format. Correction is required. See MPEP 608.01(b).

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

The application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821 through §1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given **3 (THREE)** MONTHS from the date of this letter within which to comply with the sequence rules, 37 C.F.R. §1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. §1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. §1.136. In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Applicant is requested to return a copy of the attached Notice To Comply with the response. See pages 61-62 wherein Sequence are disclosed.

Claims **1-52** have been cancelled, no claims have been amended, the disclosure has been amended, and new claims **53-62 and 63-93**** have been added as per two preliminary amendments both filed October 7, 2003. The second preliminary amendment required renumbering under the authority of 37 C.F.R. §1.126 (**). No Information Disclosure Statement (IDS) has been filed as of the mailing date of this Office action.

Claims **53-93** remain in the case.

The disclosure is objected to because of the following informalities:

The first paragraph at page 1 added by amendment is incomplete for failure to specify that the instant case is also a continuation of a PCT application (PCT/US00/20008, filed 07/21/00) according to the bibliographic data sheet for this application. Applicant is also respectfully requested to update the information concerning the filing date, patent number and issue date associated with parent case 09/856,127.

In the experimental section, the technical prefix -- deoxy -- is frequently misspelled "dexoy" in chemical names in titles and in the text. See page 51, line 19; page 52, lines 15 and 26; page 53 at lines 4, 5 and 19; etc.

In the disclosure at page 56, the title at lines 2-3 is missing the letter "o" in five separate locations.

The list of numbers and acronym in the left column at page 68 only refers to two identifiable compounds, BVDU (bromovinyldeoxyuridine) and NB 1011 (see page 56, Example 15). Examiner, and potentially the public, must know which specific compounds the remainder of the numbers are intended to identify.

The structures identified at pages 43 and 44 as being either propargylic or allylic moieties are misleading because the three structures shown with substituent formulas specify $C_3H_2$ (propargylic), but not $C_3H_5$ (allylic).

Appropriate correction is required.

35 U.S.C. §101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

Claim **62** is rejected under 35 U.S.C. §101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C.

§101. See for example *Ex parte Dunki,* 153 USPQ 678 (Bd. App. ,1967) and *Clinical Products, Ltd. v. Brenner,* 255 F. Supp. 131, 149, 149 USPQ 475 (D.D.C. 1966).

Claims **59-61 and 87-93** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have not met the written description standard of Regents of the University of California v. Eli Lilly (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)) which MPEP §2163 at page 2100-162, column 1, quotes as follows: "A definition by function alone 'does not suffice' to describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is.'" Applicant continues to rely on data at page 68 wherein the compounds are apparently only identified by number and said numbers are not otherwise associated with specific compounds anywhere else in the disclosure except for NB 1011.

Claims **59-61 and 63-93** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims extends to compounds the synthesis of which has not been defined in a manner permitting one of ordinary skill to know the identity of the compounds which have shown activity in the treatment of neoplastic disease conditions. In addition, the claim **63** identifies compounds the synthesis and biological testing of which has not been disclosed, including
i) wherein "$R^1$ is Cl, I or CN,"
ii) wherein "$R^7$ is a ... phosphodiester group or a phosphoramidite group," and
iii) "wherein the compound may be in any enantiomeric, diastereoisomeric or

stereoisomeric form, including ... L-form, α-anomeric form."
In addition, applicant has not supplied any data to support the extension of treatments to include "liver cancer."

B. The nature of the invention is directed to 5-substituted-2'-deoxyuridines and analogues thereof as defined by claims **53 and 64**, pharmaceutical compositions thereof, a method of testing for relative antineoplastic activity, and method of treating several different neoplastic disease conditions.

C. The state of the prior art is well established by the extensive lists of prior art patents and other references disclosed by the patents issued to Shepard and Shepard et al. listed on the instant PTO-892.

D. The level of one or ordinary skill is high because the practice of the invention requires knowledge of both the organic synthesis of nucleoside analogues and the medical knowledge and training required to properly administer and monitor antineoplastic agents to a host in need thereof.

E. The level of predictability in the art is limited because the number of compounds actually synthesized and/or tested, and the specific disease conditions tested, is very small when compared with the number of compounds included within the scope of the instant claims. In view of the lack complete test data, it is also unclear that the substitution of "Cl," "I" or particularly the pseudohalogen "CN" for "Br" as an X-substituent will produce equivalent biological testing results. Similarly, most of the variations provided for by the alternatives within the definitions of variables $R^6$ and $R^7$ have neither been synthesized nor tested for biological activity. And, only three neoplastic cell types have been shown to be effectively inhibited. For this reason examiner concludes that the asserted and claimed extrapolation to the effective treatment of all "pathological" cell types is not predictable and therefore not adequately enabled.

F. The amount of direction provided by the inventor is difficult to determine because of incomplete synthetic information and incomplete identifying information concerning the identity of compounds tested for biological activity at page 68. Applicant has not provided enabling support for the synthesis of "any enantiomeric, diastereomeric of stereoisomeric form," and in particular has not shown how to make

the L-forms and the α-anomers of any of the claimed compounds, or shown that the asserted and claimed pharmaceutical activity of claims **59-61 and 87-93** extends to all possible enantiomers and diastereomers of the compounds defined by claims **53 and 63**.

G. The existence of working examples is difficult to determine because of incomplete identifying information concerning either the synthesis of many of the compounds claimed or the identity of compounds tested for biological activity at page 68.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive in light of the very limited biological test results and synthetic instructions provided for the compounds defined by claims **53 and 63**. In particular, the instant method of treatment claims are only enabled for the treatment of one variety of breast cancer, one variety of colon carcinoma, and one fibrosarcoma (HT 1080; organ apparently not specified in the disclosure) according to the table at page 68. There are no enabling examples for the claimed method of testing. Therefore, examiner concludes that the amount of experimentation required to practice all aspects of the instant claimed invention is undue.

Claims **65-66, 71-74, 77-78 and 81-82** are objected to because of the following informalities:

Claims **65-66, 71-74, 77-78 and 81-82** each lack terminal punctuation.

Appropriate correction is required.

Claims **54-59, 63 and 86** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **54** the term "comprised of a mixture of the E and Z isomers" is misleading because the subject matter of claim **53** does not specifically define with "E" or "Z" the stereochemistry of either one of the double bonds in the 5-substituent, or provide for both possibilities for the double bond closest to the uracil ring. Did

applicant intend the term to read -- comprised of a mixture of the terminal halogenated double bond E and Z isomers -- or the like?

In claims **55 and 56** the term "salt" implies that there is only a single "pharmaceutically acceptable salt without identifying that particular compound. Did applicant intend the term to read -- salts --?

In claims **58 and 86** the term "A composition" is incomplete in light of the subsequent term "pharmaceutically acceptable carrier" and subject matter of claims **59-61 and 91-93**, respectively. Did applicant intend the initially noted term to read -- A pharmaceutical composition --?

In claims **57, 58 and 59**, the term "the compound" is literally incorrect because each of claims **53-56** is clearly directed to more than a single compound. In each of the initially noted claims did applicant intend the noted term to read -- a compound --?

In claim **63** the terms "phosphodiester group" and "phosphoramidate group" are indefinite because each fails to be defined in sufficient detail to permit the ordinary practitioner to determine the structural metes and bounds of the claimed subject matter.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. §101 which states that "whoever invents of discovers any new and useful process ... may obtain a patent therefor ... ." (emphasis added) Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.,* 151 U.S. 186 (1894); *In re Ockert,* 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. §101) double patenting rejection can be overcome by cancelling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. §101.

Claims **55 and 56** are rejected under 35 U.S.C. §101 as claiming the same invention as that of claims **3 and 4** of prior U.S. Patent No. **6,683,061** (PTO-892 ref. **AB**). This is a double patenting rejection.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **53-54, 57-86 and 91-93** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-2 and 5-10** of U.S. Patent No. **6,683,061** (PTO-892 ref. **AB**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claims **53-86 and 91-93** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-6 and 28-30** of copending Application Serial No. **10/119,927**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **53-86 and 91-93** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **56, 57 and 61** of copending Application Serial No. **09/782,721**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims **60-62 and 87-93** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 and 20** of copending Application Serial No. **10/051,320** (PTO-892 ref. **P3**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Some or all of claims **53-93** of this application conflict with claims **1-6 and 28-30** of copending Application Serial No. **10/119,927**, claims **56, 57 and 61** of copending Application Serial No. **09/782,721**, and claims **1 and 20** of copending Application Serial No. **10/051,320**. 37 C.F.R. §1.78(b) provides that where two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that

was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

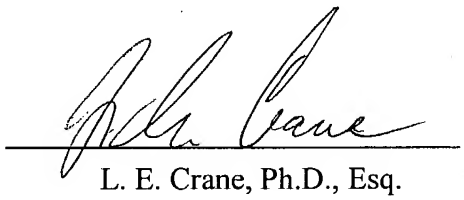
Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX directly to Examiner's computer is 571-273-0651. Telephone numbers for alternative FAX machines operated by Group 1600 are **presently unavailable**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
**02/27/2004**



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